CANADA COMMUNICABLE DISEASE REPORT

CCDR

March 5, 2015 • Volume 41•3
ISSN 1481–8531

Inside this issue: Public health issues in remote areas

Canada is a vast country which poses unique infectious disease challenges for those living in remote areas. In this issue, read about how researchers worked in Nunavut to establish baseline rates of human papillomavirus (HPV) infections prior to starting the HPV vaccine program and how a number of northern countries collaborated to establish international circumpolar surveillance to monitor invasive bacterial diseases. Consider how recent research and citizen science may have applicability in remote areas.

Surveillance

Type-specific human papillomavirus (HPV) infections and Pap test findings in Inuit and non-Inuit women in Nunavut, Canada 43
Totten S, Severini A, Jayaraman GC, Faybush ST, Johnson G, Demers AA, Sobol I, Mao Y, Wong T

Monitoring invasive bacterial diseases in the North American arctic via international circumpolar surveillance 52
Desai S, Li YA, Zulz T, Bruce M

Research

Immunogenicity and feasibility of intradermal vaccination against rabies in Quebec..... 55
Bui Y, Sow M, Cambron-Goulet E, Levac E, Milord F

Commentary

Citizen science: Exploring its application as a tool for prodromic surveillance of vector-borne disease..... 63
Hines D, Sibbald SL

Useful link

Institute of Aboriginal Peoples' Health. Canadian Institutes of Health Research. **The Pathways to Health Equity for Aboriginal Peoples**. *The Pathways initiative aims to develop the evidence base in how to design, offer and implement programs and policies that promote health and health equity.*

Call for papers

Manuscript submissions are invited for an upcoming theme issue on **Big Data**. Papers may be original research (2,500 words), or commentaries (1,500 words). See Information for Authors for submission requirements. Questions? Contact the Scientific Editor: patricia.huston@phac-aspc.gc.ca.
Submission deadline: May 15, 2015.

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

Type-specific human papillomavirus infections and Pap test findings in Inuit and non-Inuit women in Nunavut, Canada

Totten S[1*], Severini A[2], Jayaraman GC[3], Faybush ST[2], Johnson G[4], Demers AA[1], Sobol I[5], Mao Y[3], Wong T[1]

[1]Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, ON
[2]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB
[3]Centre for Chronic Disease Prevention, Public Health Agency of Canada, Ottawa, ON
[4]DynaLIFE$_{Dx}$, Edmonton, AB
[5]Nunavut Department of Health and Social Services, Nunavut

*Correspondence: stephanie.totten@phac-aspc.gc.ca

Abstract

Objective: To determine the prevalence and distribution of type-specific human papillomavirus (HPV) infections and their association with cytological outcomes in women living in the Canadian territory of Nunavut.

Methods: Surveillance of type-specific HPV infection was conducted. Cervical specimens of all Inuit, First Nations and non-Aboriginal women in Nunavut who presented for a Pap test in any clinical setting between January 2008 and March 2009 were tested for HPV infection. The association between high-grade cervical lesions and HPV type was also examined.

Results: HPV results were available for 4,043 individual women (13 to 77 years). Of those with known ethnicity (N=4,033), 89.2% were Inuit, 0.4% were First Nations and 10.4% were non-Aboriginal. First Nations women were included in all analyses except those making comparisons by ethnicity, due to the small number of individuals in this group. Overall, 29.9% of women were found to be infected with HPV (any type) and 19.9% with any high-risk HPV (type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59). Most often, women were infected with HPV 16 (6.4%) followed by HPV 31 (3.1%). There were no statistically significant differences between Inuit and non-Aboriginal (reference group) women 20 years of age and older regarding the prevalence of any HPV (odds ratios (OR): 1.19, 95% confidence intervals (CI): 0.92-1.54), high-risk HPV (OR: 1.06, 95% CI: 0.78-1.44) or HPV 16 and 18 (OR: 0.81, 95% CI: 0.51-1.27). HPV 31 was the only type that was significantly more frequent among Inuit than non-Aboriginal women (OR: 3.95, 95% CI: 1.24-12.54). There was no difference in the overall occurrence of cervical abnormalities between non-Aboriginal and Inuit women (p-value = 0.17). HPV 16 was strongly associated with cervical dysplasia, being present in 50.9% of specimens with a high-grade lesion.

Conclusion: HPV is a significant public health issue in the territory of Nunavut. The findings presented in this article are similar to those in other studies among Inuit women, with prevalence of HPV being higher than in studies conducted among non-Inuit women in other regions of Canada. These results provide a baseline of HPV prevalence that precedes the introduction of the Nunavut HPV Immunization Program in 2010 and will allow for future evaluation. The high prevalence of HPV infection among women living in Nunavut can be reduced through immunization and associated high-grade cervical abnormalities mitigated by regular cervical screening.

Introduction

Human papillomavirus (HPV), a necessary cause of cervical cancer, is estimated to be one of the most common sexually transmitted infections in Canada (1, 2). Two effective preventive vaccines have been developed and are available in Canada. The quadrivalent vaccine that protects against non-oncogenic (low-risk) HPV 6 and 11 and oncogenic (high-risk) HPV 16 and 18 was approved for use in Canada in 2006 and is offered to girls in all provinces and territories in Canada as a part of publicly-funded school-based immunization programs. In 2010 a bivalent vaccine against HPV 16 and 18 was approved for use, but it is not currently offered through publicly-funded immunization programs.

The territory of Nunavut has a young, mainly Inuit population of approximately 30,000 that is sparsely distributed across two million square kilometers in 25 communities in the circumpolar region of Canada. There are challenges in health care and public health in Nunavut. For example, compared to Canadian averages, its inhabitants are disproportionately affected by poor birth outcomes, lower life expectancy and chronic and infectious diseases, including high rates of sexually transmitted infections (3). For example, reported rates of chlamydia in Nunavut are 15 times higher than the national average and gonococcal infections are 50 times higher (4). Elevated cervical cancer incidence rates have been reported in Inuit women compared to non-Inuit women in Nunavut (8.0 vs. 5.7 per 100,000 population) (5). Development of public health strategies and programs in Nunavut aims to improve health outcomes (6), including the implementation of publicly-funded school-based HPV immunization in March 2010 for girls in grade 6 (11 to 12 years of age).

There is a paucity of data on the prevalence and type distribution of HPV infections among women in Nunavut. In 1999, a cross-sectional study that included 1,290 women in 19 Nunavut communities reported a prevalence of high-risk HPV of 26% and a prevalence of squamous intraepithelial lesions of 7.2% (7,8). These authors did not report their results by HPV type. Studies in other regions of Canada have found overall HPV prevalence rates that vary depending on population: 10.8% in women aged 18-69 in Newfoundland (9); 16.8% among women aged 13–86 in British Columbia (10); 21.8% among female university students in Montreal (11); 13.3% among women aged 15-49 in Ontario (12); 28.9% among Inuit women aged 15-69 in Nunavik, Quebec (13); 33% in women in Winnipeg (age range not reported) (14); and 24.2% among women aged 14-85 in the Northwest Territories (15).

In response to a need for baseline epidemiological data to evaluate the effectiveness of implementing a publicly-funded HPV immunization program for females, Nunavut public health authorities conducted surveillance from January 2008 to March 2009 with the objectives of determining the prevalence and distribution of HPV types in Inuit and other women living in Nunavut and examining the association between type-specific infection and cervical cytology results. This report provides the results from this surveillance initiative and the above objectives. All geographic regions of Nunavut were included in order to inform clinicians and public health practitioners throughout the territory.

Methods

Public health HPV surveillance was initiated in January 2008 under the authority of the *Public Health Act and Regulations* as executed by Nunavut's Chief Medical Officer of Health. All females presenting to any community, public health, or hospital-based clinic for cervical screening in Nunavut between January 2008 and March 2009 were included. In Nunavut, ethnicity is self-identified when individuals register with the territorial universal health care insurance plan (e.g., at birth or immigration).

Liquid-based cervical specimens were collected using BC Surepath collection kits and processed as per standard practice at the Cytopathology Laboratory at DynaLIFEDx. Leftover aliquots were forwarded to the National Microbiology Laboratory (NML) of the Public Health Agency of Canada for HPV typing. An in-house Luminex test that detects 45 HPV types was used for the HPV typing, with amplification by nested polymerase chain reaction (PGMY) primers and GP5+/GP6+) (16). The NML-Luminex method compares favourably to the commercially available Roche LinearArray genotyping method, but fewer types are detected in samples with multiple infections with more than three types. However, in this population only 3% of positive specimens (about 1% of the participants) were positive for more than three HPV types, and therefore any difference in type distribution from the Roche LinearArray would be negligible. The rare type HPV 97 was not detected by the version of the NML-Luminex method used for this study (16). HPV types were analysed according to species (as per deVilliers et al) and grouped by carcinogenic potential as assessed by the International Agency for Research on Cancer Monograph Working Group (high-risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; and probably/possibly carcinogenic: HPV 68, 26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, 97) (17, 18). HPV types were also analysed by species, in order to identify infections that include oncogenic types genetically related to the vaccine types HPV 16 and HPV 18 (species a09 and a07, respectively). Within each species, HPV types show similar biological properties and there is some evidence of cross-protection following vaccination (19).

Cytological findings were categorized using the Bethesda System: negative for intraepithelial lesion or malignancy; atypical squamous cells of undetermined significance (ASCUS); atypical squamous cells – cannot

exclude high-grade squamous epithelial lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous epithelial lesion (HSIL); squamous cell carcinoma (SCC); atypical glandular cells, not otherwise specified (AGC) (20). Cytological and HPV results were linked by a unique identifier assigned to each specimen and a sub-identifier unique to each individual was used to identify women who had more than one Pap test during the surveillance period. When more than one specimen was available for a participant, only one randomly-picked specimen was included in order to estimate the prevalence among the individual women tested, rather than among the number of specimens. Comparisons between Inuit and non-Aboriginal women were made using an age-adjusted logistic regression model with non-Aboriginal as the reference group. Data on First Nations women were not part of this analysis.

The association between the Pap result and HPV type was calculated using odds ratios (OR) and 95% confidence intervals (95% CI). The outcomes of particular interest were cytological results most likely to lead to invasive cervical cancer. To this end, ASC-H, AGC, HSIL and SCC results were combined to create a category of high-grade cervical lesions. All other cervical cytology findings were combined as low-grade cervical lesions in the logistic regression model. Specimens without valid cytology results were excluded from this analysis, but were still tested for HPV.

Results

A database of 4,683 records with valid participant identification number, cytology and HPV results was created, representing 4,043 individual females (640 "repeat" testers). Of those with known ethnicity (n=4,033), 3,596 were identified as Inuit (89.2%), 17 as First Nations (0.4%) and 420 as non-Aboriginal (10.4%).

Of those with known age (n=3,877), the median was 30 years (range: 13 to 77), 32.8% were under the age of 25. Inuit women were younger than non-Aboriginal women (median age: 29 vs. 35 years, respectively; p<0.001).

Prevalence of HPV and cervical cytological abnormalities

Of the 4,043 unique individuals, 1,207 (29.9%) tested positive for at least one HPV type, 19.9% were positive for at least one high-risk HPV and 7.5% were positive specifically for types 16 or 18, which are included in the commonly used vaccines (**Table 1**). In addition, 6.4% were positive for at least one probably carcinogenic HPV type and 9.5% tested positive for multiple HPV infections. Women under 25 years of age had the highest prevalence of HPV with 45.4% being HPV positive, compared to 30.9% in those aged 25 to 29, 23.3% in those aged 30 to 39 and 16.2% in those aged 40 and older.

Table 1: Prevalence of human papillomavirus (HPV) infection by age group among women presenting for cervical cancer screening in Nunavut, January 2008 to March 2009 (n=4,043)

Age: N		HPV Infection: N (%)				
Age Group	N for Age Group	Any type	Multiple	High-risk[1]	Probably/ possibly carcinogenic[2]	HPV 16/18
<20	521	244 (46.8)	101 (19.4)	183 (35.1)	58 (11.1)	81 (15.5)
20-24	749	333 (44.5)	118 (15.8)	245 (32.7)	73 (9.7)	96 (12.8)
25-29	621	192 (30.9)	54 (8.7)	130 (20.9)	37 (6.0)	49 (7.9)
30-39	945	220 (23.3)	59 (6.2)	133 (14.1)	41 (4.3)	45 (4.8)
≥40	1041	169 (16.2)	41 (3.9)	84 (8.1)	41 (3.9)	20 (1.9)
Missing	166	49 (29.5)	12 (7.2)	31 (18.7)	9 (5.4)	14 (8.4)
Total	4043	1207 (29.9)	385 (9.5)	806 (19.9)	259 (6.4)	305 (7.5)

[1]High risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.
[2]Probably/possibly carcinogenic: HPV 26, 53, 66, 67, 68, 70, 73, 82, 30, 69, 85.

Pap test results were available for 4,031 women of whom 92.7% had normal cytology, 5.7% were diagnosed with a low-grade cervical lesion (ASCUS and LSIL) and 1.4% with a high-grade cervical lesion (ASC-H, HSIL, AGC, or SCC). The highest rate of abnormal cytology (2.3%) was found in women aged 25 to 29 and this rate was below 2% in all other age groups (data not shown).

There were very few non-Aboriginal women less than 20 years of age that presented for cervical screening and consequently, statistical comparisons of ethnic groups did not include females less than 20 years of age. Among women 20 years of age and older, there were no statistically significant differences between Inuit and non-Aboriginal (reference group) women regarding the prevalence of any HPV (OR: 1.19, 95% CI: 0.92-1.54), high-risk HPV (OR: 1.06, 95% CI: 0.78-1.44), HPV 16 and 18 (OR: 0.81, 95% CI: 0.51-1.27), or multiple HPV infections (OR: 1.23, 95% CI: 0.73-2.06) (**Table 2**). HPV 31 is the only type that was significantly more frequent among Inuit than non-Aboriginal women (OR: 3.95, 95% CI: 1.24-12.54, data not shown). There was no difference in the overall occurrence of cervical abnormalities (p-value = 0.17) between non-Aboriginal and Inuit women (data not shown).

Table 2: Comparison of human papillomavirus (HPV) prevalence by ethnicity among Inuit and non-Aboriginal women presenting for cervical cancer screening in Nunavut, January 2008 to March 2009 (N=4,016)

HPV Result	Ethnicity[1]		OR (95% CI)[2]
	Non-Aboriginal[3] (N=420)	Inuit (N=3,596)	
Any	89 (21.2%)	1114 (31.0%)	1.19 (0.92-1.54)
Multiple	22 (5.2%)	362 (10.1%)	1.23 (0.73-2.06)
High-risk[4]	57 (13.6%)	747 (20.8%)	1.06 (0.78-1.44)
HPV 16/18	24 (5.7%)	280 (7.8%)	0.81(0.51-1.27)

[1]First Nations and Missing ethnicity excluded from analysis.
[2]OR: odds ratio; CI: confidence interval
[3]Reference group
[4]High-risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.

There were 1,207 women who were positive for any type of HPV, with a total of 1,761 infections (accounting for women positive for multiple types). Infections with species a09 were most frequent (36.9% of infections), including HPV 16 (14.7%), HPV 31 (7.1%) and HPV 58 (4.7%). Species a07 was the second most common species (21.0% of infections), of which HPV 59 (5.2%) was the most prevalent type, followed by HPV 45 (4.4%), HPV 39 (4.0%) and HPV 18 (3.2%) (**Table 3**).

Table 3: Distribution of human papillomavirus (HPV) infections by type and species among specimens positive for any type of HPV in women presenting for cervical cancer screening in Nunavut, January 2008 to March 2009 (N=1,761)[1]

Species	HPV Type	N (%)
a01	42	52 (3.0)
	32	8 (0.5)
	Total a01	60 (3.4)
a03	81	64 (3.6)
	72	46 (2.6)
	89	36 (2.0)
	62	34 (1.9)
	Total a03	258 (14.7)
a05	51	69 (3.9)
	69	8 (0.5)
	26	1 (0.1)
	82	1 (0.1)
	Total a05	79 (4.5)
a06	66	75 (4.3)
	56	47 (2.7)
	53	25 (1.4)
	30	8 (0.5)
	Total a06	155 (8.8)
a07	59	92 (5.2)
	45	77 (4.4)
	39	71 (4.0)
	18	57 (3.2)
	70	49 (2.8)
	68	17 (1.0)
	85	7 (0.4)
	Total a07	370 (21.0)
a08	40	20 (1.1)
	43	7 (0.4)
	91	1 (0.1)
	Total a08	28 (1.6)
a09	16	259 (14.7)
	31	125 (7.1)
	58	82 (4.7)
	67	58 (3.3)
	33	49 (2.8)
	52	46 (2.6)
	35	31 (1.8)
	Total a09	650 (36.9)
a10	6	53 (3.0)
	11	13 (0.7)
	44	13 (0.7)
	74	13 (0.7)
	13	7 (0.4)
	Total a11	99 (5.6)
a11	73	20 (1.1)
a13	54	27 (1.5)
a14	90	15 (0.9)

[1]The 1,207 HPV positive women had a total of 1,761 HPV infections (*i.e.* each HPV type was counted individually).

Association between HPV type and cervical cytological results

HPV 16 was the most common type, being present in 50.9% of specimens with a high-grade cervical lesion (**Table 4**, all ethnic groups combined). HPV 18 was found in 5.5% of high-grade lesions. HPV 16 was associated with the highest risk of being diagnosed with a high-grade lesion (OR=16.8, 95% CI: 9.8-29.0), followed by HPV 35 (OR=11.4, 95% CI: 3.9-34.0), HPV 45 (OR=6.7, 95% CI: 2.8-16.2) and HPV 18 (OR=4.2, 95% CI: 1.3-13.8); however, confidence intervals for these types overlapped so the differences between them are not statistically significant. Women who were positive for HPV 31, 33, 39, 51, 52, 56 and 59 were not at statistically higher risk of high-grade lesions (**Table 4**).

Table 4: Association of high-grade cervical lesions with high-risk human papillomavirus (HPV) infections, all ethnic groups combined

HPV type	Cytology			OR (95% CI)[1]
	Normal[2] (n=3,747)	Low-grade[3] (n=229)	High-grade[4] (n=55)	
	N (%)	N (%)	N (%)	
16/18	216 (5.8)	60 (26.2)	29 (52.7)	15.0 (8.7-25.7)
16	178 (4.8)	53 (23.1)	28 (50.9)	16.8 (9.8-29.0)
18	42 (1.1)	12 (5.2)	3 (5.5)	4.2 (1.3-13.8)
31	101 (2.7)	21 (9.2)	3 (5.5)	1.8 (0.6-5.9)
33	32 (0.9)	16 (7.0)	1 (1.8)	1.5 (0.2-11.2)
35	22 (0.6)	5 (2.2)	4 (7.3)	11.4 (3.9-34.0)
39	54 (1.4)	16 (7.0)	1 (1.8)	1.03 (0.1-7.6)
45	58 (1.5)	13 (5.7)	6 (10.9)	6.7 (2.8-16.2)
51	50 (1.3)	19 (8.3)	0 (0.0)	--
52	38 (1.0)	7 (3.1)	1 (1.8)	1.6 (0.2-12.0)
56	36 (1.0)	9 (3.9)	2 (3.6)	3.3 (0.8-13.9)
58	61 (1.6)	17 (7.4)	4 (7.3)	3.9 (1.4-11.1)
59	71 (1.9)	18 (7.9)	3 (5.5)	2.5 (0.8-8.2)

[1]OR: odds ratio; CI: confidence interval
[2]Reference category
[3]Low-grade lesions: atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion.
[4]High-grade lesions: atypical squamous cells – cannot exclude high-grade squamous epithelial lesion; high-grade squamous epithelial lesion; squamous cell carcinoma; atypical glandular cells, not otherwise specified.

Discussion

This analysis identified that HPV infection is more prevalent among women living in Nunavut than in many other geographical regions of Canada where HPV prevalence has been studied (9, 10, 12, 13, 15); 29.9% of all women tested during the surveillance period were positive for one or more HPV types. Of those positive, HPV 16 was the most common type (14.7% of infections) followed by HPV 31 (7.1% of infections). The prevalence of HPV infections was greatest among women less than 25 years of age of any ethnicity. The prevalence of HPV was 31.0% among Inuit women compared to 21.2% among non-Aboriginal women, but this difference was not statistically significant.

Other HPV prevalence studies conducted among women in regions of Canada with large Inuit populations have found similar results. In their cross-sectional study of HPV prevalence among Inuit and non-Inuit women aged 13 to 79 in Nunavut, Healey et al (2001) found a 25.8% prevalence of oncogenic HPV, with those aged 13 to 20 having the highest odds of infection and no statistically significant difference between Inuit and non-Inuit women (8). Hamelin-Douglas et al (2008) conducted a study among Inuit women living in Nunavik (northern Quebec), reporting a prevalence of any HPV infection of 28.9% (high-risk HPV: 20.4%); prevalence of any type of HPV was highest (58%) in those younger than 20 years of age (high-risk HPV: 46.9%) (13).

HPV 16 was associated with the highest odds of high-grade cervical lesions (ASC-H, AGC, HSIL and SCC). Although the prevalence of HPV 18 was low (1.4%), this type was associated with a significant risk of high-grade lesions. (Note: These results must be interpreted with caution due to the small number of infections detected with this type.) Approximately 52% of the specimens with high-grade lesions were positive for HPV 16 and/or 18, a finding that is consistent with other North American studies as reported in a meta-analysis by Bosch et al (2008),

who reported that the fraction of vaccine-preventable cervical cancer due to these types could be as high as 70% (21). The HPV vaccines currently in use in Canada protect against both types 16 and 18 and as such, the 2010 implementation of routine immunization for HPV in grade 6 girls in Nunavut should, in time, yield good results in reducing infection with these types and related abnormal cervical cytology. With evidence for cross-protection against related HPV types, the burden of infection with other species a07 and a09 types may be reduced as well (19, 22, 23).

Without a longitudinal component, it is not possible to determine the persistence of type-specific infections and their impact on the risk of future abnormal cervical cytology. Over half (51.4%) of the participants were 30 years of age or younger, as were the majority of women infected with high-risk or probably/possibly carcinogenic HPV. HPV infections in younger women are likely to be transient and thus may not result in a cancerous outcome (24). Future work in this population could examine persistence of type-specific infection and associated risk of high-grade cervical lesions.

No survey was administered during the surveillance period and therefore it is not possible to interpret the findings with respect to related risk factors such as sexual activity (e.g., number of partners, age of sexual debut and condom use), parity and smoking practices. These risk factors would be important to assess as cofactors in the acquisition and persistence of HPV infection in any future study conducted in this population.

There are several limitations in the surveillance methods used in this population. For example, this study represents only women who presented for Pap testing (primary screening or follow-up testing) in Nunavut between January 2008 and March 2009. Those who did not seek cervical screening may present different demographic and/or behavioural characteristics. No risk survey was used to examine cofactors for the acquisition of HPV or the development of cervical outcomes which limits the inferences that can be made. There were low numbers of observations in a number of categories used for comparison which restricts the explanatory power of the data and the relatively small number of non-Aboriginal women precludes adequate explanatory power for many sub-group analyses by ethnicity. It was not possible to perform detailed statistical analyses on First Nations women because of the small population living in Nunavut.

Conclusion

A large proportion of women who attend cervical screening in Nunavut tested positive for one or more types of HPV. Similar to other studies, HPV 16 was the most prevalent and showed the strongest association with high-grade cervical lesions. HPV 31 was the second most prevalent type, but its association with high-grade cervical dysplasia was not demonstrated.

HPV infection can be prevented with routine immunization and the associated high-grade cervical abnormalities in females can be mitigated through early detection with regular cervical screening. The results of this study provide a baseline of HPV prevalence that allows for the evaluation of the population-based HPV immunization program implemented in Nunavut in 2010, although it may take a decade or more of routine immunization with good coverage of the eligible population (grade 6 girls) before a significant impact on cervical screening results can be detected. Evaluation of public health programs such as HPV immunization can lead to evidence-informed interventions and improved health outcomes for the women of Nunavut.

Acknowledgements

The authors gratefully acknowledge the contribution of the Nunavut Department of Health and Social Services, Nunavut health care professionals and the women of Nunavut to this important surveillance initiative.

Conflict of interest

None

Funding

None

References

(1) International Agency for Research in Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. 2007:670.

(2) Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189;12-19.

(3) Public Health Agency of Canada. Ontario/Nunavut Agency Regional Office Annual Report 2006-07. Ontario/Nunavut Agency Regional Office, Public Health Agency of Canada; 2007. http://publications.gc.ca/collections/collection_2012/aspc-phac/HP2-8-2007-eng.pdf.

(4) Jayaraman G, Totten S, Perin M, Fang L, Remes O. Report on sexually transmitted infections in Canada: 2008. Ottawa: Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada; 2010. http://publications.gc.ca/collections/collection_2011/aspc-phac/HP37-10-2008-eng.pdf.

(5) Healey S, Plaza D, Osborne G. A ten-year profile of cancer in Nunavut. Iqaluit: Government of Nunavut; 2003. http://pubs.aina.ucalgary.ca/health/55692E.pdf.

(6) Nunavut Department of Health and Social Services. Developing healthy communities: A public health strategy for Nunavut 2008-2013. Iqaluit: Government of Nunavut; 2008. http://www.gov.nu.ca/sites/default/files/files/Public%20Health%20Strategy%20-%20English%20final.pdf.

(7) Healey SM, Aronson K, Mao Y, Franco EL. Human papillomavirus and cervical dysplasia in Nunavut: Prelude to a screening strategy. Int J Circumpolar Health. 2004;63:(2):199-201.

(8) Healey SM, Aronson KJ, Mao Y, Schlecht NF, Mery LS, Ferenczy A, et al. Oncogenic human papillomavirus infection and cervical lesions in aboriginal women of Nunavut, Canada. Sex Transm Dis. 2001;28:694-700.

(9) Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. Cancer Epidemiol Biomarkers Prev. 2000;9:945-951.

(10) Moore RA, Ogilvie G, Fornika D, Moravan V, Brisson M, Amirabbasi-Beik M, et al. Prevalence and type distribution of human papillomavirus in 5,000 British Columbia women—implications for vaccination. Cancer Causes Control. 2009;20:1387-1396.

(11) Richardson H, Franco E, Pintos J, Bergeron J, Arella M, Tellier P. Determinants of low-risk and high-risk cervical human papillomavirus infections in Montreal University students. Sex Transm Dis. 2000;27:79-86.

(12) Sellors JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. CMAJ. 2000;163:503-508.

(13) Hamlin-Douglas LK, Coutlée F, Roger M, Franco EL, Brassard P. Prevalence and age distribution of human papillomavirus infection in a population of Inuit women in Nunavik, Quebec. Cancer Epidemiol Biomarkers Prev. 2008;17:3141-3149.

(14) Young TK, McNicol P, Beauvais J. Factors associated with human papillomavirus infection detected by polymerase chain reaction among urban Canadian Aboriginal and non-Aboriginal women. Sex Transm Dis. 1997;24:293-298.

(15) Jiang Y, Brassard P, Severini A, Goleski V, Santos M, Leamon A, et al. Type-specific prevalence of Human Papillomavirus infection among women in the Northwest Territories, Canada. J infect Public Health. 2011;4:219-227.

(16) Zubach V, Smart G, Ratnam S, Severini A. Novel microsphere-based method for detection and typing of 46 mucosal human papillomavirus types. J Clin Microbiol. 2012;50:460-464.

(17) Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens—Part B: biological agents. Lancet Oncol. 2009;10:321-322.

(18) De Villiers E, Fauquet C, Broker TR, Bernard H, Zur Hausen H. Classification of papillomaviruses. Virology. 2004;324:17-27.

(19) Bonanni P, Boccalini S, Bechini A. Efficacy, duration of immunity and cross-protection after HPV vaccination: A review of the evidence. Vaccine. 2009;27:A46-A53.

(20) Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. J Am Med Assoc. 2002;287:2114-2119.

(21) Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, et al. Epidemiology and natural history of Human Papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine. 2008;26:K1-K16.

(22) Brown DR, Kjaer SK, Sigurdsson K, Iversen O, Mauricio H, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis. 2009;199:926-935.

(23) Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow S, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. Lancet. 2009;374:301-314.

(24) Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomarkers Prev. 2003;12:485-490.

Monitoring invasive bacterial diseases in the North American Arctic via the International Circumpolar Surveillance Project

Desai S[1*], Li YA[1], Zulz T[2], Bruce M[2]

[1]Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON
[2]National Center for Emerging Zoonotic and Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

*Correspondence: shalini.desai@phac-aspc.gc.ca

Abstract

This paper summarizes the most recent Invasive Bacterial Diseases (IBD) Working Group meeting of the International Circumpolar Surveillance (ICS) project. The ICS is a population-based surveillance network for invasive bacterial diseases that provides a mechanism to determine changes in incidence rates and antimicrobial resistance. The meeting took place in Montreal, Canada on February 12-13, 2014. Data were included from participating Canadian provincial and territorial jurisdictions as well as from the State of Alaska. This report is based on the audio records of the meeting as well as the meeting presentations.

The ICS IBD Working Group focuses on invasive diseases caused by: *Streptococcus pneumoniae* (Sp), *Neisseria meningitidis* (Nm), *Haemophilus influenzae* (Hi), Group A Streptococcus (GAS) and Group B Streptococcus (GBS). Data on invasive disease caused by each of these organisms were reviewed through December 2012-2013. Although the incidence of some of these vaccine-preventable invasive diseases has decreased, emergence of *H. influenzae* serotype a (Hia) in both Alaska and Northern Canada was noted. An interlaboratory quality control (QC) program is ongoing to monitor laboratory proficiencies for serotyping.

Introduction

Surveillance for invasive bacterial diseases provides valuable information on their incidence, severity and laboratory characteristics. The International Circumpolar Surveillance (ICS) System's Invasive Bacterial Diseases (IBD) Working Group falls within the mandate of the Sustainable Development Working Group of the international Arctic Council (1). The ICS System is an international collaboration of numerous working groups that investigate and study issues relevant to the circumpolar north (2). This paper provides a brief overview of the ICS System and its collaborative work and provides information on the most recent meeting of the Invasive Bacterial Diseases Working Group which took place in February 2014.

Background

The ICS System was founded in 1999 as a collaboration between Canada and the US Arctic (Alaska) to strengthen surveillance of invasive pneumococcal disease among circumpolar residents who were experiencing a higher incidence of this disease with a large proportion of isolates demonstrating antimicrobial resistance compared to US and Canadian residents living in southern regions (2). The system has continued to expand over the next one and a half decades and as of 2015, includes surveillance for invasive disease caused by *Streptococcus pneumoniae* (Sp), *Haemophilus influenzae* (Hi), *Neisseria meningitides* (Nm), Group A Streptococcus (GAS) and Group B Streptococcus (GBS) in Canada (the Territories, Newfoundland and Labrador and northern Quebec), the United States of America (Alaska), Greenland, Iceland, Norway, Sweden and Finland (3, 4, 5, 6).

The northern regions of the circumpolar countries share many common factors such as demographics (small population size), geography (large areas but sparsely populated, challenges in accessing medical care that may

necessitate transfer of patients to more urban locations), climate (extreme weather) and social issues (isolation, cultural differences). All of these factors make them more similar to one another than to inhabitants in the southern regions of their own countries. Of the eight countries in the circumpolar north, Russia does not participate in IBD surveillance but does take part in other ICS initiatives such as surveillance for tuberculosis (7).

The ICS network is a unique collaboration within the circumpolar north which combines population-based surveillance with epidemiological and laboratory linkages. Cases based on standard case definitions are identified by public health in each jurisdiction once laboratory confirmation is available and epidemiological data such as age, gender, clinical illness and risk factors have been collected in collaboration with local providers. The system is population-based in each participating country and provides epidemiological information on individual cases as well as laboratory data. These data are nominally linked within a jurisdiction and then de-identified to become a part of the overall surveillance system. Data are owned by each jurisdiction and compiled at the CDC Arctic Investigation Program in Alaska. These two factors (population based surveillance with epidemiological and laboratory linkages), make it a unique collaboration within the circumpolar north. The group meets annually either by WebEx or face-to-face in order to discuss current epidemiologic trends and to provide a forum to discuss invasive bacterial disease issues faced in the circumpolar north.

The 2014 meeting of the ICS IBD Working Group

The February 2014 ICS IBD Working Group meeting took place in Montreal, Canada. Participants represented Canada and US. Members from other countries were unable to attend.

The goal of the annual meeting is to review ICS IBD data to better understand the epidemiology of the five invasive bacterial diseases under surveillance. The February 2014 meeting focused on data from 1999 to 2012/2013. Data from the five regions in Canada (Nunavut, Northwest Territories, Yukon, Northern Quebec, Northern Labrador) participating in the collaboration were presented as well as data from the State of Alaska.

Canadian ICS data from 1999 to 2012 were reviewed by organism, serotype, year, age, region, ethnicity and clinical manifestation. Compared with Canadian national rates, the average incidence rates of invasive diseases caused by Sp, Hi, Nm, GAS were much higher in the Canadian ICS regions. Incidence rates of GBS were not compared due to differences in case definition; ICS reports GBS in all ages where national data includes only the neonatal age group. In the ICS regions, Aboriginal residents had higher incidence rates of invasive pneumococcal disease, Hi and invasive GAS (iGAS) than non-Aboriginals. For invasive pneumococcal disease and invasive meningococcal disease (IMD), incidence rates were highest among children under two years of age. Regional differences were noted in the overall incidence of invasive pneumococcal disease and Hi. Invasive GAS was the only disease that showed an increasing trend over the surveillance period; with the most affected groups being children less than two years of age and those over 65 years of age. The case fatality ratio was highest for IMD and lowest for GBS.

Alaskan data from 2000 to 2013 were reviewed with a focus on the data from 2011 to 2013. Data were stratified by organism, year, age, ethnicity and serotype. While IMD decreased over the surveillance period, invasive GAS and GBS showed an increasing trend Alaska Natives had much higher incidence rates of all targeted diseases compared with non-Alaska Natives. In reviewing cases of *H. influenzae*, Hia accounted for the majority of cases among children less than five years old whereas Hi non-typeable accounted for most cases among individuals five years and older. GBS is notifiable in all ages in Alaska.

The ICS Interlaboratory Quality Control Program was established in 1999 as a means to test the comparability of data submitted via different methods employed by the laboratories in the network. The Quality Control Program initially compared results for Sp serotyping and antimicrobial susceptibility testing and has expanded to include Nm serogrouping, Hi serotyping and iGAS *emm* typing results. Serotyping data for GBS is not collected by ICS, therefore its inclusion in the Quality Control Program is not necessary. This Quality Control Program has shown a high degree of correlation among the centers (8, 9). This provides added confidence that differences or similarities in the data are likely due to true differences in epidemiology between countries rather than aberrant results due to different laboratory methods.

Conclusion

The ICS is a unique and successful international collaboration providing population-based surveillance that includes both laboratory and epidemiological data on disease targets. The network is able to provide valuable information on existing and emerging invasive bacterial diseases as disease patterns change. Based on the most recent Invasive Bacterial Disease Working Group meeting, invasive Hia is seen as an emerging pathogen in the North American Arctic. Further work is planned to characterize the virulence and clinical severity of disease of this organism.

Acknowledgements

The authors gratefully acknowledge all participants in the ICS network as well as the following meeting participants: Christine Cash (Government of Yukon – Department of Health and Social Services), Kianoush Deghani (Cree Board of Health and Social Service of James Bay - Public Health Department), Sylvia Keefe Doody (Labrador Health Centre - Labrador-Grenfell Health Region), Heather Hannah (Government of Northwest Territories), Brigitte Lefebvre (Laboratoire de santé publique du Québec), Angela Mullen (Government of Nunavut - Department of Health), Nadine Abboud, Annie-Claude Bourgeois (ICS TB Co-Chair), Jenne Cunliffe, Walter Demczuk, Irène Martin, Monique St-Laurent and Raymond Tsang from the Public Health Agency of Canada, Karen Rudolph and Prabhu Gounder from the Center for Disease Control and Prevention National Center for Infectious Diseases .

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention and the Public Health Agency of Canada.

Conflict of interest

None

Funding

None

References

(1) The Arctic Council. The Arctic Council Secretariat. http://www.arctic-council.org/index.php/en/.

(2) Parkinson A, Bruce MG, et al. International circumpolar surveillance: A network for the surveillance of infectious diseases in the Arctic. EID. 2008 Jan;14(1):18-24.

(3) Helferty M, Rotondo JL, Martin I, Desai S. The epidemiology of invasive pneumococcal disease in the Canadian North from 1999 to 2010. Int J Circumpolar Health. 2013 Aug;72.

(4) Bruce MG, Deeks S, et al. The International Circumpolar Surveillance System for Population-based Surveillance of Invasive Pneumococcal Disease 1999-2005. EID. 2008 Aug;14(1):25-33.

(5) Bruce MG, Deeks S, et al. Epidemiology of *Haemophilus influenzae* serotype a in the North American Arctic, 2000-2005. EID. 2008 Jan;4(1): 48-55.

(6) Bruce MG, Zulz T, et al. The epidemiology of invasive Group A streptococcal infection in the North American Arctic, 2000-2006. Clinical Microbiology and Infection. 2008 May;14(s7):483 P2049.

(7) Zulz T, Parkinson A, et al. International circumpolar surveillance: Prevention and control of infectious diseases: 1999-2008. IJCH. 2009;4.

(8) Reasonover A, Zulz T, et al. The International Circumpolar Surveillance Interlaboratory Quality Control Program for *Streptococcus pneumoniae*, 1999 to 2008. J Clin Micro. 2011 Jan;49(1):138-43.

(9) Tsang R, Rudolph K, et al. International Circumpolar Surveillance Interlaboratory Quality Control Program for Serotyping *Haemophilus influeanzae* and Serogrouping *Neisseria meningitidis*, 2005 to 2009. J Clin Micro. 2012 Mar;50(3):651-6.

Immunogenicity and feasibility of intradermal vaccination against rabies in Quebec

Bui Y[1, 2,3*], Sow M[3], Cambron-Goulet E[2], Levac E[2], Milord F[1, 2,3]

[1]Institut national de santé publique du Québec, Montréal, QC
[2]Direction de santé publique de la Montérégie, QC
[3]Université de Sherbrooke, Sherbrooke, QC

*Correspondence author: yen.bui.agence16@ssss.gouv.qc.ca

Abstract

Objectives: Preexposure vaccination against rabies is recommended for some travellers and individuals exposed to the virus through their work. At a cost of at least $150 per intramuscular (IM) dose, few follow this recommendation. In Canada, provided certain conditions are met, the National Advisory Committee on Immunization (NACI) and the Comité d'immunisation du Québec allow a more economical alternative, intradermal vaccine administration (ID) which uses 1/10 the IM dose. The purpose of this study is to assess the feasibility and immunogenicity of intradermal preexposure vaccination.

Methods: Students and employees at the Faculty of Veterinary Medicine received three doses of ImovaxRage™ (Sanofi Pasteur) inactivated, human diploid cell rabies vaccine at days 0, 7 and 21 or 28. An IM or ID booster dose was administered after two years when indicated.

Outcomes: Among the 159 participants who received three doses, 139 underwent serological testing in the year following vaccination and all achieved protective antibody levels. The antibody level was higher when measured within five weeks of the third dose. When the serological control was performed two years later, 65% of participants had a <0.5 IU/ml titre. Of the 22/30 participants who chose an ID booster, 100% responded and the average antibody titres were multiplied by 11, indicating a strong anamnestic response.

Discussion: ID rabies vaccination is immunogenic, economic and could be considered for the booster dose. Protective antibodies decline rapidly after primary immunization by ID, so it would seem prudent to perform a serological control one year later on individuals at high risk of occult occupational exposure. An alternative would be to give these individuals a routine ID booster dose one year after primary vaccination, which would simplify initial treatment and reduce related costs (follow-up, blood sampling, serological tests, etc.). The persistence of protective antibodies after this booster dose should be assessed to determine the need for subsequent serological tests and the ideal interval between tests.

Introduction

Rabies is an infection caused by a rhabdovirus of the *Lyssavirus* genus. It is transmitted through contact with the saliva of an infected mammal, usually by a bite. There is no way to diagnose the disease prior to its clinical stage (1). The virus causes acute, progressive encephalomyelitis, which is almost invariably fatal once symptoms appear, except in very rare cases where individuals manage to survive (2).

Worldwide, more than 50,000 rabies-related deaths are reported every year. Most cases are caused by dog bites and occur in Asia, Africa and South America. India alone accounts for 20,000 rabies-related deaths per year (1). Travellers who visit areas where rabies is highly endemic are at risk, especially if they travel in rural areas (3). In several European countries, most reported human cases are imported and occur among travellers (4).

In Canada, only 24 cases of human rabies were reported from 1924 to 2009 (5) and the last three cases were attributed to bats. Moreover, most cases of rabies occur through contact with an infected bat (6,7), even though the red fox is the main reservoir of terrestrial rabies. Although cases of animal rabies in Canada decreased from 670 in 2000 to 141 in 2012 (8), the animal reservoir of rabies is still extensive (5). People who have contact with animals in their work, such as veterinarians, are at higher risk of exposure to the rabies virus.

In addition to intramuscular (IM) administration, the World Health Organization (WHO) allows intradermal (ID) administration of rabies vaccines that are prepared in cell culture or embryonated eggs, provided they contain 2.5 IU per dose (6,9). This measure is used primarily in developing countries to promote use of these postexposure vaccines, which cost more, but are much more effective and cause far fewer severe side effects than vaccines prepared from animal nerve tissue (1, 6). A protocol for postexposure ID vaccination was introduced for the first time in Thailand in 1984 and subsequently implemented successfully in various countries including India, the Philippines, Sri Lanka and Thailand (10, 11).

Both the WHO and the National Advisory Committee on Immunization (NACI) in Canada endorse ID administration of preexposure rabies vaccine. This practice reduces the costs of preexposure vaccination, which is not funded by the Canadian public health system because each dose of the vaccine costs between $150 and $180. It also simplifies postexposure procedures, eliminating the need for rabies immunoglobulin and reduces the required number of vaccine doses from four to two (12).

In Quebec, vaccination is governed by the *Protocole d'immunisation du Québec* (PIQ), which was produced by Quebec's Ministry of Health and Social Services and endorsed by a scientific advisory committee, the Comité d'immunisation du Québec. Under PIQ, preexposure rabies vaccines can be administered with a 0.1-ml ID dose or a 1-ml IM dose, using either of the two vaccines approved in Canada, RabAvert™ (Novartis) purified chick embryo cell rabies vaccine, or ImovaxRage™ (Sanofi Pasteur) human diploid cell rabies vaccine, both recognized as immunogenic and considered interchangeable (13). ID administration requires good technique to avoid subcutaneous injection and storage regulations and aseptic technique must be followed (6). In addition, according to the *Canadian Immunization Guide* and PIQ, a serological test is required after ID vaccination for documenting immune response because no ID formulation is approved in Canada. Finally, it is more economical to vaccinate multiple individuals at each session. For all these reasons, this route of administration is seldom used.

Several studies throughout the world have demonstrated the immunogenicity of intradermal preexposure vaccination (14, 15, 16, 17). In addition, the increase in antibody levels achieved by administering an IM or ID booster dose in individuals who previously received ID vaccination is similar to that achieved in individuals who previously received IM vaccination, indicating a good anamnestic response (18, 19).

The aim of this study was to assess the immunogenicity and feasibility of ID rabies vaccination in Canada. This could systemize the availability of the vaccine portfolio to risk groups and improve access to the rabies vaccine.

Methodology

The Université de Montréal Faculty of Veterinary Medicine in St-Hyacinthe, Quebec, Canada has a service agreement with the Richelieu-Yamaska Health and Social Services Centre (CSSS) to offer preexposure rabies ID vaccination at a lower cost to the Faculty's students and employees. In the fall of 2006, participants were recruited by letter, on a voluntary basis to receive the ID rabies vaccine. Pregnant women, individuals under 18, previously vaccinated individuals, those with a history of severe allergic reaction to a previous dose of the vaccine or one of its components, as well as people taking or beginning to take chloroquine within one month after vaccination were excluded.

ImovaxRage™ (Sanofi Pasteur) vaccine was utilized. It is a freeze-dried human diploid cell vaccine (HDCV), containing 2.5 IU/ml (13). Given the absence of formulations for ID injection in Canada, vaccination sessions involved sufficient numbers of participants to allow single-dose 1-ml vials to be split into 0.1-ml doses. In accordance with PIQ, vaccines were stored between 2 and 8°C and no doses were administered more than six hours after the product was reconstituted. A strict aseptic technique was used.

Written consent was obtained at the time of vaccination along with permission to send the research team information on immunization dates, demographic data, follow-ups and serological test results. Experienced nurses with good ID injection technique vaccinated participants at the Faculty of Veterinary Medicine between September 11 and November 6, 2006. Three 0.1-ml doses were administered in the deltoid muscle on days 0, 7, 21 or 28. A

telephone and mail reminder system was introduced. A form was used to gather demographic information on participants and serious or unexpected clinical events occurring after vaccination.

An initial serological test was prescribed from two to four weeks after the third dose of the vaccine, which is the interval recommended by PIQ (13) to confirm immunity. For people whose antibody assay was less than 0.5 IU/ml, an additional dose of the vaccine by IM or ID was offered. A second serological test was recommended for these people to confirm adequate immune response.

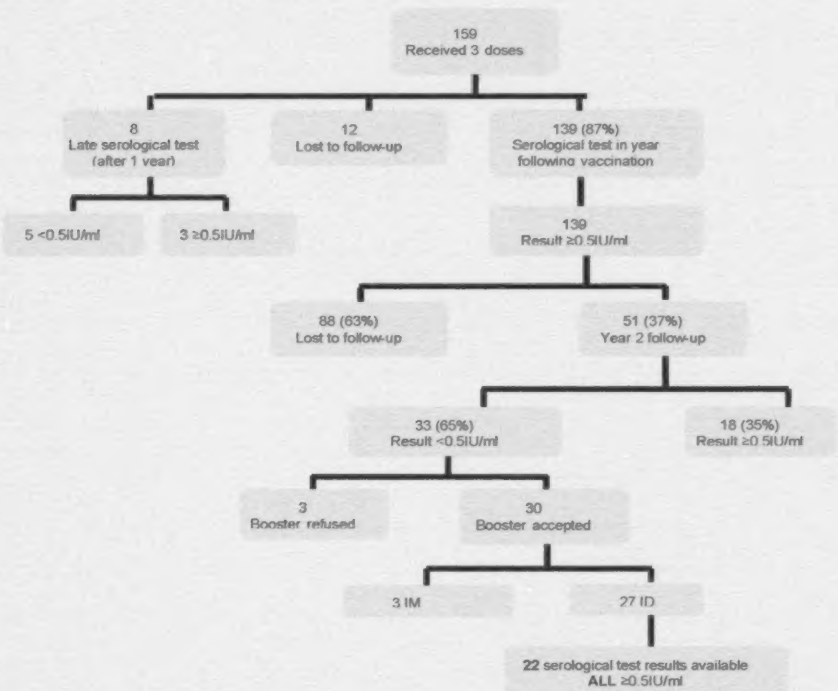
For those who had an adequate immune response, a serological control was performed two years after completion of the vaccine series to verify antibody persistence. At this stage, the subjects could choose to receive an ID or IM booster dose if their antibody assay was less than 0.5 IU/ml. All antibody assays were performed in Toronto at the Canadian national rabies reference laboratory using the rapid fluorescent-focus inhibition test (RFFIT).

The chi-square test or t-test was used to monitor the demographics of participants and to compare those lost to follow-up. The correlation between the time of the first serological test and the antibody assay was measured using the Pearson coefficient. A significance level of 0.05 was used for the analyses and 95% confidence intervals (CIs) were calculated where appropriate. The research protocol for this study was approved by the Richelieu-Yamaska CSSS's Ethics Research Committee.

Outcomes

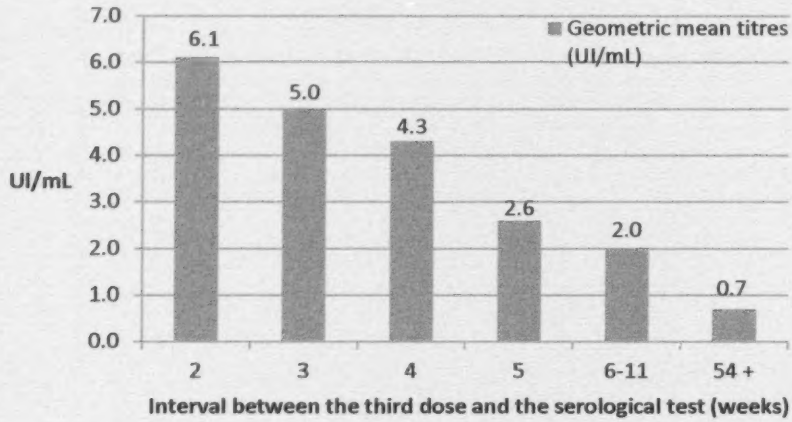
A total of 159 Faculty of Veterinary Medicine students and employees received the three doses of vaccine (**Figure 1**) and agreed to allow their information to be sent to the research team. The subjects were 18 to 59 (mean of 23 and median of 22) years of age and 84% were women. No serious or unexpected clinical events after vaccination were reported.

Figure 1: Flowchart of participant follow-ups



The result of the first serological test was available for 147 people (**Figure 2**), 139 of who had their serological test within one year of completion of the vaccine series, with an interval ranging from two to 11 weeks between the third vaccine dose and the serological test. Those who had their serological tests done two weeks after the third dose had a 6.1 IU/ml mean antibody concentration, while this concentration averaged 2.6 IU/ml if the serological test was performed five weeks after the third dose. There is a negative correlation in the time between the third dose and antibody concentration antibodies: $r=-0.31$; $p<0.05$. Of the eight people who had their serological test done one year or more after vaccination (the deadline was up to 161 weeks), five had a score <0.5 IU/ml.

Figure 2: Geometric mean titres (IU/ml) based on time after third dose (N=147)



Of the 139 participants (87%) who had their serological test done in the first year (from 2 to 11 weeks after the 3rd dose), 100% achieved a ≥0.5 IU/ml rabies antibody titre (**Table 1**). Two years after completion of the vaccination series, 51 participants reported for serological control. Although there was a general decrease in antibodies between the first and second serological tests, 35% (18/51) still had a protective level of rabies antibodies. According to the results available for 22 participants who agreed to have the ID booster, 100% achieved rabies antibody levels ≥0.5 IU/ml and there was a sharp increase in antibody concentrations (**Table 1**). There was no difference in the average age of participants who reported for follow-up and those lost to follow-up (22 versus 24 years of age, $p = 0.44$) and the percentage of women (82% versus 85%, $p = 0.63$).

Table 1: Antibody titre (IU/ml) after the 3rd dose, at the serological control two years later and after the booster dose

Variables	First serological test (2-11 weeks after the 3rd dose)	Follow-up serological testing after 2 years	Serological test after booster dose
Number of cases	139	51	22
Average concentration of antibody titres (IU/ml) [95% CI]	5.3 [4.9 – 5.7]	0.74 [0.4 – 1][1]	4.8 [4.1 – 5.5]
Range	0.6 – 10.0	0.1 – 5.7	1.5 – 7.4
Protective antibody titre	100% (139/139)	35% (18/51)	100% (22/22)

[1]Excluding a participant who showed an increase in antibody levels between the first and second serological test.

Discussion

To the authors' knowledge, this is the first study on intradermal preexposure rabies vaccination published in Canada. A total of 159 participants received a series of three 0.1-ml doses of ImovaxRage™ (Sanofi Pasteur) ID vaccine. No serious adverse effects were noted and it appears that improved injection techniques and the efficacy

and safety of new generations of rabies vaccines have decreased the negative side effects that were observed following ID administration in the past (20,21). All participants who completed a serological test in the year following the third dose had protective levels of rabies antibodies. These results confirm that ID administration of rabies vaccine is safe and immunogenic in healthy people.

A rapid decrease in antibody titres was observed if the serological test was performed more than five weeks after primary immunization. This study did not include an IM control group to measure whether the route of administration influences the kinetics of the immune response. Some studies have reported that the titres achieved after primary immunization and booster dose were higher by IM than by ID (18, 22, 23). However, the protective antibody level obtained would be as adequate by ID as by IM (6, 21). In addition, it is known that cell culture rabies vaccines provide excellent immune memory and several studies have demonstrated an anamnestic response after a booster dose in individuals previously vaccinated by ID (19,24,25,26).

The results of this study demonstrate that two years after primary immunization, rabies antibodies persist at varying levels, with 35% of subjects still showing a protective titre. After administration of the booster dose, 100% of participants for whom serological test results were available developed an anamnestic response with mean antibody titres multiplied by 11. All participants in this study were 18 years of age and older and a large majority were women, reflecting the demographics of the students in the Faculty of Veterinary Medicine. No significant differences between age and sex groups were identified in this study nor in the literature (26). The demographics of participants lost to follow-up were similar to those of participants who completed the study.

Several studies have shown that memory response to a booster dose may be induced years after primary immunization, even among those whose antibody titres fell below the 0.5 IU/ml threshold considered protective (26, 27). Malerczyk et al reported an anamnestic response to a booster dose in individuals vaccinated 15 years earlier (25) and other studies report an anamnestic response to a booster dose to up to 21 years after primary immunization (6).

In recent years, the emergence of rabies was observed in southern Quebec with the migration of a new strain of raccoon rabies from the United States (27, 28). Participants in this study were veterinary students working in an enzootic area. However, the results of this study revealed that antibody levels declined rapidly after the third dose and that a number of recipients already had titres below 0.5 IU/ml one year after primary immunization. A systematic review conducted in England reported that up to 13% of recipients' antibody levels decreased to <0.5 IU/ml one year after IM primary immunization (29). Since antibody titres may be lower with the ID route (25, 26), antibodies are expected to decrease more quickly after the vaccine is administered through this route. The results point in the same direction suggesting that for groups at risk of occult exposure, the date of the first serological control and administration of the 1st booster dose be moved up from two years to one year. This recommendation would ensure that these individuals' antibody titres do not fall below the protective threshold.

Currently, it takes at least six to eight weeks to obtain serological test results. In addition, patient follow-ups and reminders for blood samples require substantial resources and the number of patients lost to follow-up remains problematic (63% in this study). More studies are needed to document the persistence of protective antibodies after ID primary immunization and after an ID booster dose, but it is likely that an ID booster administered after one year could provide protection long enough (5) to extend the time between subsequent serological controls.

It also appears that cell culture vaccines are highly immunogenic and protective antibody titres after a booster dose can last up to five years in 96.2% of cases (5, 6). Research has shown that a booster dose administered one year after the primary immunization series could induce protective antibodies lasting up to 10 years (30) and that subjects who achieved a titre ≥30 IU/ml could receive a booster every 10 years and every three years for those with a titre <30 IU/ml. This course of action would eliminate the need for serological tests every two years.

Five participants who completed their serological test one year or more after the third dose achieved a result below the protective threshold. With the data provided in this study, it is not known whether this is a primary failure of vaccination or an expected gradual decline in antibody concentrations over time. Given the excellent immune response in 139 participants who completed their serological tests during the first year, it is assumed that if serological testing had been done sooner after primary immunization, those five individuals could have achieved an adequate antibody level.

The economic benefits of this injection route were directly observed during vaccination sessions. A 1-ml vial of rabies vaccine was sufficient to vaccinate seven to eight people intradermally. The CSSS established the cost per dose of ID vaccine at $60, three times less than for an IM dose. The net savings calculation should take into account the cost of nursing time required for the ID technique, the costs of serological tests, follow-ups and results monitoring. It was also observed that 90% of participants whose rabies antibody level was <0.5 IU/ml after two years, chose to receive the booster dose via the ID route, even if they had to complete another serological test to document the response.

It is also known that few travellers get the rabies vaccine, e.g., a study at Bangkok Airport involving 7,681 foreign travellers revealed that only 12% had completed their vaccination series, 15% received one or two doses, while 73% had not been vaccinated at all (31). The risk of being bitten when travelling in endemic areas is difficult to assess. A study involving 1,882 tourists visiting Thailand for an average of 17 days estimated that 1.3% of them had been bitten (32). It is essential to reduce costs in order to make the vaccine more readily available to groups with occupational risk, such as the study participants or travellers in endemic areas. Another benefit of preexposure vaccination is that travellers bitten while abroad would no longer need rabies immunoglobulins, which are either in very short supply or unavailable in most developing countries (6) and recipients would also require fewer vaccine doses for postexposure. In addition, travellers, who are not considered at risk of occult exposure to the rabies virus, do not have to receive a booster dose or undergo repeated serological controls.

Other intradermal preexposure vaccination schedules were studied around the world, such as simultaneous administration of two ID injections (one in each deltoid area) at days 0, 7, 21 or 28, at days 0, 3, 7 or only at day 0 (19). Regardless of the schedule, a strong anamnestic response was observed one year later, after two booster vaccinations. Although empirical, it is likely that these practices would be helpful in cases where high-risk travellers are scheduled to leave shortly and there is not enough time to perform serological tests.

In November 1982, a U.S. Peace Corps volunteer in Kenya completed preexposure rabies prophylaxis with a standard three dose intradermal (ID) series of human diploid cell rabies vaccine (33). In May 1983, she was bitten by a dog, but did not consult a health professional for postexposure vaccination and subsequently died of rabies. A serological test performed when her symptoms appeared revealed an inadequate antibody titre. At the same time, serological tests performed on other Peace Corps volunteers who also received ID vaccination revealed that nine of the 11 subjects had inadequate antibody titres. Although response after primary vaccination did not seem adequate, the survey considered that if two doses had been administered postexposure as recommended the death could have been avoided. This highlights the importance of serological control after primary intradermal vaccination to ensure antibody levels are ≥ 0.5 IU/ml. This incident and the recall of three lots of an approved rabies ID vaccine with insufficient antigen levels, led to the withdrawal of ID vaccines from the US market in 2001, even if the immunogenicity of the ID route was not called into question (3).

Intradermal vaccination is still offered at the Université de Montréal Faculty of Veterinary Medicine. Between 2007 and 2013, nearly 1,000 people were vaccinated and serological tests performed two to four weeks after the third dose produced only two results <0.5 IU/ml (0.36 and 0.47 IU/ml, respectively) (Jocelyne Angers, personal communication, July 2014). This route is always well tolerated and RabAvert™ and ImovaxRage™ vaccines are used interchangeably during vaccination sessions which facilitates vaccine stock management.

The results of this study demonstrate that administering the vaccine intradermally using $1/10^{th}$ of the IM dose is an immunogenic, economic and feasible alternative where groups of clients can be scheduled for vaccination by qualified staff using good techniques and when there is enough time for post-vaccination serological testing. All these conditions were fulfilled in this study at the Faculty of Veterinary Medicine. Because antibody titres decline rapidly during the first year, it would be prudent to provide individuals at high risk of occult exposure to rabies with a booster dose one year after primary vaccination without prior serological testing. Serological follow-up to document the persistence of antibodies should be performed subsequently to determine the need and most appropriate time for other booster doses.

Availability of an approved ID formulation in Canada and shorter serological test times would ease the logistical problems encountered in this study.

Acknowledgements

The authors would like to thank the students and staff at the Université de Montréal Faculty of Veterinary Medicine for their contribution to this study. A big thank you is also extended to the entire Richelieu-Yamaska CSSS team and in particular to Francine Lord and Danielle Bisson for logistics. Anne-Marie Clouâtre, Dr. Lina Perron and Dr. Louise Lambert of the Direction de santé publique de la Montérégie are also acknowledged with gratitude for providing a critical review of the project and Nathalie Bernier and Marianne Picard-Masson for their various analyses.

Conflict of interest

None

References

(1) World Health Organization. Rabies vaccines. Wkly Epidemiol Rec. 2010;85(32):309-20.

(2) Willoughby RE, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, Chusid MJ, Rupprecht CE. Survival after treatment of rabies with induction of coma. N Engl J Med. 2005;352(24):2508-14.

(3) Rupprecht CE, Shlim DR. Rabies. In: Centers for Disease Control and Prevention (CDC). CDC Health Information for International Travel 2014. New York: Oxford University Press, 2014:270-6.

(4) Comité consultatif de la médecine tropicale et des voyages. Déclaration relative aux voyageurs et au vaccin contre la rage. RMTC2002;28. http://www.collectionscanada.gc.ca/webarchives/20071116052847/. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/02vol28/28sup/dcc4.html

(5) Agence de santé publique du Canada. Guide canadien d'immunisation. Partie 4 – Vaccins inactivés, Vaccins contre la rage. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-rabi-rage-fra.php#voyageurs. (Available in English: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-rabi-rage-eng.php).

(6) World Health Organization. WHO expert consultation on rabies. World Health Organ Tech Rep Ser. 2005;931:1-88. http://whqlibdoc.who.int/trs/WHO_TRS_931_eng.pdf.

(7) De Serres G, Dallaire F, Côte M, Skowronski DM. Bat rabies in the United States and Canada from 1950 through 2007: Human cases with and without bat contact. Clin Inf Dis. 2008;46:1329–37.

(8) Agence canadienne d'inspection des aliments. Cas de rage positifs au Canada – Rage chez les animaux. http://epe.lac-bac.gc.ca/100/206/301/cfia-acia/2011-09-21/www.inspection.gc.ca/francais/anima/disemala/rabrag/statsf.shtml.

(9) World Health Organization. Updated WHO position paper on rabies vaccines. Geneva: WHO; 2010. http://www.who.int/immunization/Rabies_slides_Aug_2010.pdf.

(10) Chulasugandha P, Khawplod P, Havanond P, Wilde H. Cost comparison of rabies preexposure vaccination with postexposure treatment in Thai children. Vaccine. 2006;24(9):1478-82.

(11) Quiambao BP, Dimaano EM, Ambas C, Davis R, Banzhoff A, Malerczyk C. Reducing the cost of postexposure rabies prophylaxis: Efficacy of 0.1 ml PCEC rabies vaccine administered intradermally using the Thai Red Cross postexposure regimen in patients severely exposed to laboratory-confirmed rabid animals. Vaccine. 2005;23(14):1709-14.

(12) Comité national consultatif de l'immunisation. Mise à jour sur les vaccins antirabiques. RMTC. 2005;31.

(13) Ministère de la santé et des services sociaux du Québec. Protocole d'immunisation du Québec – 6e édition. Québec: Gouvernement du Québec; 2013.

(14) Lau C, Sisson J. The effectiveness of intradermal preexposure rabies vaccination in an Australian travel medicine clinic. J Travel Med. 2002;9(6):285-8.

(15) Wilde H, Briggs DJ, Meslin FX, Hemachudha T, Sitprija V. Rabies update for travel medicine advisors. Clin Infect Dis. 2003;37(1):96-100.

(16) Ranney M, Partridge R, Jay GD, Rozzoli DE, Pandey P. Rabies antibody seroprotection rates among travelers in Nepal: "Rabies seroprotection in travelers". J Travel Med. 2006;13(6):329-33.

(17) Bui YG, Milord F, Levac E, Lord F. Faisabilité de la vaccination intradermique contre la rage au Québec. Communication par affiche présentée aux 10e Journées annuelles de santé publique. Montréal (QC); 2006.

(18) Jijaroensup W, Limusanno S, Kwawplod P, Serikul K, Chomchay P, Kaewchomphoo W, Tantawichien T, Wilde H. Immunogenicity of rabies postexposure booster injections in subjects who had previously received intradermal preexposure vaccination. J Travel Med. 1999;6:234-37.

(19) Khawplod P, Wilde H, Benjavongkulchai M, Srianroon C, Chomchey P. Immunogenicity study of abbreviated rabies preexposure vaccination schedules. J Travel Med. 2007;14(3):173-6.

(20) Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S, Wasi C. Réponse en anticorps après vaccination antirabique de post-exposition par de petites doses intradermiques de vaccin purifié préparé sur cellules d'embryon de poulet ou sur cellules Vero. Bull World Health Organ. 2000;78:693–8.

(21) World Health Organization. WHO position paper on rabies vaccine – Table III: Safety of cell-culture-based rabies vaccines. Geneva; 2010. http://www.who.int/immunization/rabies_grad_safety.pdf.

(22) Kositprapa C, Limsuwun K, Wilde H, Jaijaroensup W, Saikasem A, Khawplod A, Kri-aksorn U, Supich C. Immune response to stimulated postexposure rabies booster vaccinations volunteers who received preexposure vaccinations. Clin Inf Dis. 1997;25:614-6.

(23) Nicholson KG, Turner GS, Aoki FY. Immunization with a human diploid cell strain of rabies virus vaccine: Two-year results. J Infect Dis. 1978;137(6):783-8.

(24) Suwansrinon K, Wilde H, Benjavongkulchai U, Lertjarutorn S, Boonchang S, Suttisri R, Khowplod P, Daviratanasilpa S, Sitprija V. Survival of neutralizing antibody in previously rabies vaccinated subject: A prospective study showing long lasting immunity. Vaccine. 2006;24(18):3878-80.

(25) Malerczyk C, Briggs DJ, Dreesen DW, Banzhoff A. Duration of immunity: An anamnestic response 14 years after rabies vaccination with purified chick embryo cell rabies vaccine. J Travel Med. 2007;14(1):63-4.

(26) Brown D, Featherstone JJ, Fooks AR, Gettner S, Lloyd E, Schweiger M. Intradermal preexposure rabies vaccine elicits long lasting immunity. Vaccine. 2008;26:3909–12.

(27) Chang HG, Eidson M, Noonan-Toly C, Trimarchi CV, Rudd R, Wallace BJ, Smith PF, Morse DL. Public health impact of reemergence of rabies, New York. Emerg Infect Dis. 2002;8(9):909-13.

(28) Blanton JD, Dyer J, McBrayer J, Rupprecht CE. Rabies surveillance in the United States during 2011. J Am Vet Med Assoc. 2012;241(6):712-22.

(29) Morris J, Crowcroft NS. Preexposure rabies booster vaccinations: A literature review. Dev Biol (Basel). 2006;125:205-15.

(30) Strady A, Lang J, Lienard M, Blondeau C, Jaussaud R, Plotkin SA. Antibody persistence following preexposure regimens of cell-culture rabies vaccines: 10-year follow-up and proposal for a new booster policy. J Inf Dis. 1998;177:1290-5.

(31) Piyaphanee W, Kittitrakul C, Lawpoolsri S, Gautret P, Kashino W, Tangkanakul W, Charoenpong P, Ponam T, Sibunruang S, Phumratanaprapin W, Tantawichien T. Risk of potentially rabid animal exposure among foreign travelers in Southeast Asia. PLoS Negl Trop Dis. 2012;6(9):e1852. doi: 10.1371/journal.pntd.0001852.

(32) Phanuphak P, Ubolyam S. Should travelers in rabies endemic areas receive preexposure rabies immunization? Presentation at the International Conference on Travellers' Medicine. Atlanta (GA); 1991.

(33) Bernard KW, Fishbein DB, Miller KD, Parker RA, Waterman S, Summer JW, Reid FL, Johnson BK, Rollins AJ, Oster CN et al. Preexposure rabies immunization with human diploid cell vaccine: Decreased antibody responses in persons immunized in developing countries. Am J Trop Med Hyg. 1985;34(3):633-47.

Citizen science: Exploring its application as a tool for prodromic surveillance of vector-borne disease

Hines D[1*], Sibbald SL[1, 2, 3]

[1]The Schulich Interfaculty Program in Public Health, Western University, London, ON
[2]Department of Medicine, Western University, London, ON
[3]School of Health Studies, Western University, London, ON

*Correspondence: dhines6@alumni.uwo.ca

Abstract

Citizen science is the systematic collection and analysis of data, development of technology, testing of natural phenomena and the dissemination of these activities by researchers on a primarily avocational or voluntary basis. The application of citizen science-informed mobile applications (apps) provides a means for Canadians to participate in the surveillance of infectious disease.

This article makes the case for a mobile application that can be used to enhance the surveillance of vector-borne diseases in Canada. Lyme disease is used as an example due to its increasing incidence and lack of available real-time information. The authors also suggest how such an app could be designed and used in a way that would attract end users to download and use it as a public health tool. If successful, these type of apps could serve as supplements to active surveillance programs as well as a means for bidirectional communication between public health professionals and citizens.

Introduction

In the past decade, climate change and public health have become inextricably linked (1). A recent survey, reported that over 81% of Canadians were concerned about health risks associated with climate change. The same survey showed that 49% of Canadians felt climate change increased the incidence of infectious disease (2). As the Canadian climate continues to warm, tick and other vector populations are beginning to increase, most notably in areas such as Southern British Columbia and Ontario (3). Lyme disease is the most common vector-borne zoonosis in North America and is on the rise across Canada. It was estimated that in 2010, 18% of the population of Eastern and Central Canada were living in areas at risk of Lyme disease and this percentage is projected to increase (4,5).

The *Ixodes* black legged tick known to carry the Lyme disease causing bacteria *Borrelia burgdorferi*, is distributed across Canadian deciduous or mixed forests habitats (6). In addition to Lyme disease, cases of vector-borne diseases uncommonly identified in Canada are beginning to present closer to Canadian borders. For example, in 2014 the United States Centers for Disease Control and Prevention (CDC) reported the first cases of two tickborne diseases (Powassan virus, known to produce long-term neurological problems and Anaplasmosis, a disease with typical symptoms of fever and headache) in the Great Lakes region (7).

Infectious disease surveillance in Canada has successfully identified the appearance and spread of infectious diseases such as Influenza H1N1, H7N9, SARS, Lyme disease and others. Increasing available 'real-time' information on these diseases could improve public health officials' understanding of a potential outbreak and also provide public education. Ideally, the collection of real-time information should be a collective effort. The recent Ebola outbreak has led to exploration of how smartphone user activity could be used to track disease spread (8). At this time smartphone user activities are monitored retroactively, whereas citizen science could inform processes for real-time monitoring of disease spread (8).

Citizen science has been defined by Kinder as, "the systematic collection and analysis of data, development of technology, testing of natural phenomena and the dissemination of these activities by researchers on a primarily avocational basis" (9). Simply put, it is citizen observations or data that is collected on a volunteer basis. Citizen science is a fairly new term, but is an old practice (10, 11). In recent years, researchers have used citizen science, in their work to support findings described in publications or presentations (10, 12, 13).

Incorporating citizen involvement in the surveillance or raising awareness of vector-borne disease, such as Lyme disease, could be a novel form of citizen science. This could be achieved through the use of a mobile phone application designed to collect information on vector habitats or breeding grounds. To the authors' knowledge, a smartphone app allowing for bidirectional flow of vector-borne disease information (from end user to administrator and vice versa), has not yet been developed (14).

It is proposed that citizen science-informed applications should be developed to raise awareness of notifiable vector-borne disease. In doing so, they could empower the community and aid in the protection of public health. This commentary explores how the collective power of smartphone users could be harnessed to support awareness and surveillance of vector-borne disease.

Analysis

It is very difficult to accurately track vector-borne diseases, such as Lyme disease in real-time (i.e., the actual time during which an event occurs). Tracking and identifying areas endemic with *Ixodes* blacklegged ticks carrying *B. burgdorferi* requires a significant number of hours and is often challenged by many other competing demands on public health officials. This challenge could be reduced by recruiting the assistance of public citizens in collecting this information. Engaging citizens via mobile applications where citizens can observe natural events and be linked to scientific research on a particular vector-borne disease provides an opportunity for public participation in the protection of public health.

Smartphone usage among Canadian adults (18-65 years of age) is on the rise. In 2013, a Google report estimated that 56% of adults were using a smartphone, up from 33% in early 2012 (15). Google Canada indicated smartphone users "are using their mobiles to change the way they communicate with others and specifically trying to understand the world around them" (16). The increased use of mobile devices and their applications has expanded Canadians' ability to participate in and protect the health of their communities. Mobile applications grounded in the concepts of citizen science (9) present a viable option to mobilize citizens in the surveillance of and awareness-raising efforts about vector-borne diseases.

Citizen science, mobile applications and health

Smart phone technology allows a natural extension of citizen science with the added benefit of being real-time. Much like the call for citizens to scan millions of images for clues in an attempt to solve the case of the missing Malaysian Airlines plane (17), incorporating citizen science functionality into a mobile application would provide an opportunity for citizens to engage in real-time prodromic (pre-diagnostic health information) vector-borne disease surveillance and potentially provide warnings for impending public health concerns.

An example of an app developed for infection surveillance is *Flu near You* designed by HealthMap at Boston's Children Hospital (18). This is a community-driven flu-tracking site that provides real-time information to the public. Another example of a public health-oriented app is ***ImmunizeON***, an app designed to monitor, track and remind Ontarians of their immunization schedules (19). The app maintains vaccination records, alerts end users about immunization schedules and informs them about potential harms related to defective vaccines or other events of public health significance through the use of banners. *ImmunizeON* is an excellent app for monitoring and tracking, but it does not promote the collection and submission of observations and data. The communication function between end users and public health officials remains limited to emails through an external site and there is no user interface which allows for direct communication through the app itself. A citizen science-informed app would expand the communication functionality to include a way to allow submissions from end users back to public health.

The primary function of a citizen science-based Lyme disease app would be to provide citizens with information on how to identify ticks and their habitats. The Lyme disease mobile app developed by the Eastern Ontario Health

Unit provides information on symptoms of Lyme disease, physical characteristics of the ticks and what to do if bitten (20), but it does not include the feedback loop to help track where ticks are located. By adding a geotagging capability (that is, the ability to track the exact geographic location of ticks), the end user could tag and take photos of prospective pathogen-carrying ticks. The final layer of functionality would be to have public health officials engage with the tags/photos in real-time. When public health officials receive submissions, a team of trained professionals could identify whether the submission warrants further investigation (i.e., is in fact a pathogen-carrying tick species). To the authors' knowledge, current available apps do not include the function of allowing citizens to submit photos or data.

Citizen science allows end users to interact with health professionals and submit observations that professionals themselves would not be able to. In the case of *ImmunizeON*, prodromic surveillance of potential adverse effects related to defective vaccines is possible by embedding a two-way communication functionality (i.e., In-App Messaging). A number of successful citizen science projects have been launched that demonstrate the potential of citizen science apps, such as National Moth Week 2014, which promotes contributing photos and data to online databases and Drexel University's Dr. Dan Duran's Elderberry Longhorn Beetle Project (13).

Theoretically, a citizen science-informed surveillance app, complete with diagnostic criteria for the vector in question, would allow citizens to confidently identify risk areas for ticks. This would occur as citizens were engaging in activities such as (hiking, hunting, gardening, etc.) in yards, parks or forests in or near known risk areas.

Application development

According to Google's *Mobile Movement Report*, 82% of smart phone users in Canada use their smart phones to research and read news and 27% look up health-related information. Smartphone users currently accessing health-related information would be a prime target audience for a citizen science-based app. However, the promotion for this application should be open to all who are interested as citizen science is not meant to focus solely on individuals or groups with subject knowledge. A citizen science-based app should be user friendly and targeted to even the most novice smartphone user.

Considerations

There are several key considerations when developing and launching a citizen science initiative (21). The first is the issue of incentives for use. Citizen science for the purposes of awareness and data/information collection is considered avocational and distinct from work that is compensated (9). Much of the software or "freeware" is distributed at no cost to the consumer with little or no restrictions on use (12). Attaching incentives (monetary or other) to the citizen science activity might increase participants' use, but would also introduce potential unintended consequences such as engagement for monetary gain (22).

"Gamifying" or the use of game design elements in non-game contexts (23) is a second consideration. By making the app fun to use, gamifying can help gain traction with participants by maintaining their engagement (24) as well as attracting and retaining users (23).

A third consideration is the promotion of the app. Usage of traditional multimedia advertising (television, social media, print ads etc.) and Web 2.0 (such as blogs and online forums) are reliable methods of promotion. Innovative social marketing tools such as RSS feeds (Rich Site Summary or Really Simple Syndication – broadcasting information to external websites) are also useful in engaging a broad target audience.

There are other questions to consider when developing a platform for any citizen science-based tool. For example: Who will be responsible for managing the information (a vendor or public health agency? Who will fund the initiative (local, national private)? How will results be disseminated back to the end user and the broader public?

Conclusion

Canada is witnessing an increase in vector-borne diseases due to climate change, modification of the ecology and other factors. A citizen science-informed mobile application could provide a creative medium to disseminate learning tools about vectors and vector-borne diseases and to interact with Canadians. Citizen science also has the potential to empower Canadians and maximize their ability to contribute to knowledge creation and health surveillance. If successful, a Lyme disease app could serve as a template to track other similar vector-borne disease (for example: Powassan virus and Anaplasmosis).

Citizen science is gaining traction in the mobile application and the academic sector and there are opportunities to explore its use in public health. Since an app to track and monitor vector-borne diseases has to the authors' knowledge, not been developed or evaluated, we cannot be sure that it would be successful, however we do know from the study of citizen science and through the use of other similar applications that engaging the community in this way could provide valuable potential in monitoring and raising awareness.

This commentary is part of a larger discussion around public participation in infectious disease surveillance. During disease outbreaks or pandemics, members of society may feel powerless and often rely on healthcare authorities for guidance and protection. Increased use of mobile devices in the Canadian population coupled with the rise of mobile news apps and social media could provide a point of access to augment capacity for real-time infectious disease surveillance.

Acknowledgements

Many thanks to Michel Deilgat for his excellent input and support on earlier versions of this article. Delaney Hines would like to thank the Master of Public Health program within the Schulich School of Medicine and Dentistry at Western University for arranging the placement opportunity at the Centre for Food-borne Enteric, Zoonotic and Infectious Disease at the Public Health Agency of Canada, where much of the ideas in this paper were developed.

Conflict of interest

None

Funding

None

References

(1) Maibach EW, Nisbet M, Baldwin P, Akerlof K, Diao G. Reframing climate change as a public health issue: An exploratory study of public reactions. BMC Public Health. 2010;10(1): 299.

(2) Akerlof K, Debono R, Berry P, Leiserowitz A, Roser-Renouf C, Clarke K, Rogaeva A, Nisbet MC, Weathers MR, Maibach EW. Public perceptions of climate change as a human health risk: Surveys of the United States, Canada and Malta. Int J Environ Res Public Health. 2010;7(6):2559-606.

(3) Public Health Agency of Canada [Internet]. Lyme disease and other tickborne diseases: Information for healthcare professionals. Ottawa: Government of Canada; 2014. http://www.phac-aspc.gc.ca/id-mi/tickinfo-eng.php#sec-2.2.

(4) Leighton PA, Koffi JK, Pelcat Y, Lindsay LR, Ogden NH. Predicting the speed of tick invasion: An empirical model of range expansion for the Lyme disease vector Ixodes scapularis in Canada. J Appl Ecol. 2012;49:457–464.

(5) Ogden NH, Radojevic M,Wu X, Duvvuri VR, Leighton PA, Wu J. Estimated effects of projected climate change on the basic reproductive number of the Lyme disease vector Ixodes scapularis. Environ Health Perspect. 2014;122(6): 631-38. http://ehp.niehs.nih.gov/1307799/.

(6) Hatchette TF, Davis I, Johnston BL. Lyme disease: Clinical diagnosis and treatment. CCDR. 2014;40(11):194-208. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-11/dr-rm40-11-lyme-1-eng.php.

(7) Centers for Disease Control and Prevention [Internet]. Tickborne diseases of the U.S. Atlanta: Centers for Disease Control and Prevention, 14 July 2014. http://www.cdc.gov/ticks/diseases/.

(8) Talbot D. Cell-phone data could help predict Ebola's spread [Internet]. Boston: MIT Technology Review; 22 Aug. 2014. http://www.technologyreview.com/news/530296/cell-phone-data-might-help-predict-ebolas-spread/.

(9) Kinder J. Engaging Canadians in citizen science. Canadian Government Executive. 2014;20(4):15. http://www.canadiangovernmentexecutive.ca/category/item/1543-engaging-canadians-in-citizen-science.html.

(10) Iii F, Mims M. Amateur science: Strong tradition, bright future. Science. 1999;284(5411):55-56. http://www.sciencemag.org/content/284/5411/55.full.

(11) Feyerabend P. Science in a free society. 4th ed. Vol. 31. London: Verso; 1978. p. 385-90.

(12) Cornell Lab of Ornithology - Citizen Science Central [Internet]. Defining citizen science. Ithaca: National Science Foundation; 2014. http://www.birds.cornell.edu/citscitoolkit/about/definition.

(13) Scientific American [Internet]. Citizen science. New York: Scientific American; 2014. http://www.scientificamerican.com/citizen-science/.

(14) Benedict M, Geleta D. Development of ClickClinica: A novel smartphone application to generate real-time global disease surveillance and clinical practice data. BMC Medical Informatics and Decision Making. 2013;13(1):70-80. http://www.biomedcentral.com/1472-6947/13/70.

(15) Ipsos MediaCT [Internet]. Our mobile planet: Canada - Understanding the mobile consumer. Google, May 2013. http://think.withgoogle.com/mobileplanet/en/.

(16) Canadian Broadcasting Corporation [Internet]. Smartphone use way up in Canada, Google finds. 29 July 2013.

(17) Martinez M, Williams D, Simon D. Crowdsourcing volunteers comb satellite photos for Malaysia Airlines jet. Cable News Network, 12 Mar. 2014

(18) American Public Health Association [Internet]. Flu near you: Do you have it in you? 20 Oct. 2014. https://flunearyou.org/about/.

(19) Wilson K, Atkinson K, Pluscauskas M, Bell C. A mobile-phone immunization record in Ontario: Uptake and opportunities for improving public health. J Telemed Telecare. 2014;1(5). http://www.ncbi.nlm.nih.gov/pubmed/25084770.

(20) Ontario Agency for Health Protection and Promotion (Public Health Ontario). Vector-borne diseases 2013 summary report. Toronto: Queen's Printer for Ontario; 2014. http://www.publichealthontario.ca/en/eRepository/Vector_Borne_Diseases_Summary_Report_2013.pdf.

(21) Archer G. Crowdsourcing: Improve healthcare with the brainpower of millions [Internet]. Action For Better Healthcare. 15 May 2014. http://actionforbetterhealthcare.com/crowdsourcing-improve-healthcare-brainpower-millions/.

(22) Kumagai D. Exploiting digital workers through global crowdsourcing. U of T News. Toronto: University of Toronto;11 Mar. 2014.

(23) Deterding S, Dixon D, Khaled R, Nacke L. From game design elements to gamefulness: Defining gamification, In: Proceedings of the 15th International Academic MindTrek Conference: Envisioning future media environments. 2011;9(15). http://gamification-research.org/2012/04/defining-gamification/.

(24) Von Bargen T, Zientz C, Haux R. Gamification for MHealth: A review of playful mobile healthcare. Stud Health Technol and Inform. 2014;225(28). http://www.ncbi.nlm.nih.gov/pubmed/25000057.